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Health and Environmental Effects Profile for Methyl Ethyl Ketone

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16. ABSTRACT

The Health and Environmental Effects Profile for methyl ethyl ketone was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Methyl ethyl ketone has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for methyl ethyl ketone is 3.2 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for methyl ethyl ketone is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHYL ETHYL KETONE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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LIST OF ABBREVIATIONS

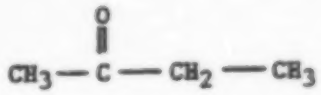
ADI	Acceptable daily intake
BCF	Bioconcentration factor
BODT	Biochemical oxygen demand, theoretical
CAS	Chemical Abstract Service
COD	Chemical oxygen demand
CS	Composite score
DL	Distal motor latency
EC_{50}	Effective concentration to 50% of recipients (and to all other subscripted concentration levels)
GC/MS	Gas chromatography/Mass spectrometry
GI	Gastrointestinal
K_{oc}	Soil sorption coefficient
K_{oh}	Rate constant for reaction with hydroxyl radical
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MCV	Motor nerve conduction velocity
MED	Minimum effective dose
MNCV	Mixed nerve conduction velocity
ppb	Parts per billion
ppm	Parts per million
RD_{50}	Concentration which causes a 50% decrease in respiratory rate
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TWA	Time-weighted average
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Methyl ethyl ketone is also known as 2-butanone and MEK. The structure, molecular weight, and empirical formula for methyl ethyl ketone are as follows:

Structure:



Molecular weight: 72.11

Empirical formula: C_4H_8O

The CAS Registry number for methyl ethyl ketone is 78-93-3.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methyl ethyl ketone is a colorless stable liquid with a characteristic acetone-type odor (Papa and Sherman, 1981). It is highly miscible with many conventional organic solvents and is known for its excellent solvency of a wide variety of resinous compounds. Selected physical properties are listed below:

Melting point:	-85.9°C	Papa and Sherman, 1981
Boiling point:	79.57°C	Papa and Sherman, 1981
Specific gravity:	0.8062 (20/20°C)	Papa and Sherman, 1981
Refractive index:	1.3780 (20°C)	Papa and Sherman, 1981
Vapor pressure, mm Hg:		
at 20°C	77.5	Mackay et al., 1982
at 25°C	98.0	Mackay et al., 1982
Water solubility:		
at 90°C	190,000 ppm	Verschueren, 1983
at 10°C	353,000 ppm	Verschueren, 1983
at 20°C	268,000 ppm	Papa and Sherman, 1981
Flashpoint:	-6°C	Papa and Sherman, 1981

Conversion factors (air):	1 mg/m³ = 0.340 ppm 1 ppm = 2.94 mg/m³	Verschueren, 1983
Henry's Law Constant: (atm-m³/mol)		
at 20°C	$2.92/3.23 \times 10^{-5}$	Mackay et al., 1982
at 25°C	4.35×10^{-5}	Mackay et al., 1982
at 25°C	$4.16/6.11 \times 10^{-5}$	Rathban and Tai, 1982
Log octanol/water partition constant:	0.29	Hansch and Leo, 1981

Methyl ethyl ketone undergoes chemical reactions typical of carbonyl groups with active hydrogen atoms on adjacent carbon atoms, and it condenses with a variety of reagents (Papa and Sherman, 1981).

1.3. PRODUCTION DATA

Methyl ethyl ketone is currently being produced by the following manufacturers (CMR, 1984):

Manufacturer/Location	Annual Capacity (10^6 lbs)
ARCO Chem. (Channelview, TX)	65
Celanese (Pampa, TX)	90
Exxon (Bayway, NJ)	300
Shell (Norco, LA)	230

Union Carbide also has a plant in Brownsville, TX with a production capacity of 85 million pounds/year, which can be called into operation if necessary. Domestic production of methyl ethyl ketone in 1982 and 1983 was reported to be 468.4 and 531.4 million pounds, respectively (USITC, 1983, 1984).

ARCO, Exxon and Shell manufacture methyl ethyl ketone by the dehydrogenation of 2-butanol (SRI, 1984). The first step in this vapor-phase dehydrogenation process is the hydration of butenes to yield 2-butanol; the second step involves the use of copper or zinc catalysts at high temperatures to accomplish the dehydrogenation (Papa and Sherman, 1981).

Celanese and Union Carbide manufacture methyl ethyl ketone as a by-product of butane oxidation (SRI, 1984). This process involves the liquid-phase oxidation of butane to yield an acetic acid product and a methyl ethyl ketone by-product (Papa and Sherman, 1981).

1.4. USE DATA

Uses for methyl ethyl ketone and the percent distribution for these uses are listed in Table 1-1, which shows that methyl ethyl ketone is used predominantly as a volatile solvent.

TABLE 1-1

Uses for Methyl Ethyl Ketone and their Percent Distribution*

Use	Percent Distribution
Solvent for coatings (vinyl, acrylic, nitrocellulose, miscellaneous)	55
Adhesives solvent	14
Magnetic tapes (cleaning)	6
Printing inks solvent	4
Lube oil dewaxing	4
Intermediates	4
Export	13

*Source: CMR, 1984

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of methyl ethyl ketone in the environment depends on the ability of the compound to undergo chemical, photochemical and biological reactions and to transport or partition from one environmental matrix into another.

2.1. WATER

2.1.1. Hydrolysis. Ketones are generally resistant to hydrolysis (Lyman et al., 1982). Although kinetic rates are not available, environmental hydrolysis of methyl ethyl ketone is not expected to be important.

2.1.2. Oxidation. Methyl ethyl ketone is stable to molecular oxygen (O_2) (Lande et al., 1976); therefore, reaction with dissolved O_2 in water is not likely to occur. Oxidants, however, are generated in aquatic environments by sunlight-induced photochemical mechanisms (Mabey et al., 1981). Two such oxidants are the hydroxyl radical (•OH) and alkyl peroxyl radical (RO_2•). Anbar and Neta (1967) reported that the rate constant for the reaction of methyl ethyl ketone with •OH in aqueous solution (pH 7) at room temperature is 5.4×10^8 M^{-1} sec^{-1}. Assuming an ambient •OH concentration of 10^{-17} M, a half-life of ~4 years can be calculated. Dorfman and Adams (1973) reported an •OH rate constant of 9×10^8 M^{-1} sec^{-1} at pH 6-7 which would result in a half-life calculation closer to 2 years, which is still not significant. Hendry et al. (1974) reported that the rate constant for the reaction of methyl ethyl ketone with RO_2• in the liquid-phase at 30°C is 0.055 M^{-1} sec^{-1}. Assuming that the RO_2• concentration in sunlit natural bodies of water is 10^{-9} M, a half-life of ~400 years is calculated. Therefore, the available data indicate that methyl ethyl ketone oxidation in the aquatic environment is not important.

2.1.3. Photolysis. Kinetic rate data regarding the photolysis of methyl ethyl ketone in the ambient aquatic environment were not located in the available literature as cited in the Appendix. Methyl ethyl ketone, however, can undergo significant direct photolysis in the atmosphere (Section 2.2.). This suggests that direct photolysis of methyl ethyl ketone in water is possible. In addition, methyl ethyl ketone has been reported to be an effective photosensitizer for the photolysis of various chlorinated hydro- carbons (Augustyniak, 1978; Golub, 1971). Methyl ethyl ketone has been shown to undergo significant photolysis in cyclohexane solution irradiated with 310 nm light (Somersall and Guillet, 1972) and in water and various polar solvents that are subjected to 248 nm radiation (Encinas et al., 1980).

2.1.4. Microbial Degradation. A number of studies examined the biodegradation of methyl ethyl ketone in laboratory tests using activated sludge, sewage, or wastewater inocula as a source of microorganisms. These tests predominantly indicate that methyl ethyl ketone is readily degraded by these microbes. Speece (1983) found that methyl ethyl ketone was biodegradable by industrial anaerobic wastewater treatment technology. Using a filtered wastewater seed, Bridie et al. (1979) measured a methyl ethyl ketone 5-day BODT of 83% and COD of 95%. Dojlido (1979) used an activated sludge to measure a 100% degradation of methyl ethyl ketone in 8 days at a concentration of 200 ppm and in 9 days at 400 ppm; a 10% BODT was observed in 0.5 days. The rate of methyl ethyl ketone biodegradation was found to increase rapidly with the acclimitization of the microorganisms (Dojlido, 1977). By measuring gas production from the Hungate Serum Bottle Technique, Chou et al. (1979) noted 100% methyl ethyl ketone anaerobic degradation with enriched methane cultures. Dore et al. (1975) examined methyl ethyl ketone degradation using a 5-day BOD test (AFNOR T 90/103) with inocula from three

polluted surface waters and noted a 48% BODT. Price et al. (1974) used a filtered sewage seed to study methyl ethyl ketone degradation in freshwater and in saltwater. In freshwater, 5- and 20-day BODTs of 76 and 89%, respectively, were obtained. In saltwater, the 5- and 20-day BODTs were 32 and 69%, respectively. Buzzell et al. (1968,1969) and Young et al. (1968) found that methyl ethyl ketone readily degraded with sewage and activated sludge in BOD tests. With a Warburg respirometer, Gerhold and Malaney (1966) observed a 3.1% BODT (24 hours) in activated sludge. Gaudy et al. (1963) found methyl ethyl ketone readily degradable in activated sludge, while Heukelekian and Rand (1955) measured a 5-day BODT of 88% in the sewage seed test.

Methyl ethyl ketone degradation has been reported in pure culture studies using microbes isolated from soils (Phillips and Perry, 1974; Perry, 1968; Eubanks, 1973). Various species of the hydrocarbon-utilizing Mycobacteria are able to grow on methyl ethyl ketone (Lukins and Foster, 1963). The bacterial species, Alcaligenes faecalis, however, which is isolated from activated sludge, did not significantly degrade methyl ethyl ketone (Marion and Malaney, 1963).

Methyl ethyl ketone has been shown to be a metabolite formed during the microbial oxidation of the corresponding alkane and secondary alkanol (Lijmbach and Brinkhuis, 1973; Patel et al., 1980, 1983; Hou et al., 1979; Lukins and Foster, 1963).

2.1.5. Transport.

2.1.5.1. VOLATILIZATION -- Rathbun and Tai (1982) measured the overall mass-transfer coefficient for the volatilization of methyl ethyl ketone from water in a stirred laboratory bath. At ~25°C, the experimental mass-transfer coefficient ranged from 0.306-0.611 m/day at the stirring rates

used (557-2020 rpm). Assuming a 1 m water depth, volatilization half-lives of 27-54 hours can be calculated from these coefficients. The authors also used their experimental data to produce a Henry's Law Constant in the range of $4.16\text{-}6.11 \times 10^{-5}$ atm-m³/mol; this value of Henry's Constant suggests that volatilization is significant in all environmental waters (Lyman et al., 1982).

Mackay et al. (1982) also used laboratory apparatus to experimentally derive Henry's Constant for methyl ethyl ketone to be 4.35×10^{-5} atm-m³/mol at 25°C, which agrees with the Rathbun and Tai (1982) study. Hine and Mookerjee (1975) measured the equilibrium ratio of methyl ethyl ketone in gas-phase to methyl ethyl ketone in water-phase at 25°C in a dilute methyl ethyl ketone aqueous solution system to be 0.0019; this is the unitless Henry's Law Constant that can be converted to 4.6×10^{-5} atm-m³/mol.

These data indicate that volatilization of methyl ethyl ketone from the aquatic media can be expected to be an important removal mechanism. The rate of removal will be dependent upon the body of water contaminated. Removal from a typical river can be expected to occur more rapidly than from a typical lake.

2.1.5.2. **ADSORPTION** -- Adsorption to particulate organic matter and sediment in the aquatic environment is not expected to be significant because of the high water solubility and low K_{ow} of methyl ethyl ketone.

2.1.5.3. **BIOACCUMULATION** -- The BCF of an organic compound can be estimated from the K_{ow} by using the following equation developed by Veith et al. (1980): Log BCF=0.76 Log K_{ow}-0.23. The BCF value for methyl ethyl ketone is calculated to be ~1. Prediction from the WS can be done by using the Kenaga and Goring (1978) equation: Log BCF=2.791-0.564 Log WS. The BCF for methyl ethyl ketone (WS=268,000 ppm) is calculated to be ~0.5. These

BCF values indicate that methyl ethyl ketone will not bioaccumulate significantly in aquatic organisms.

2.2. AIR

Methyl ethyl ketone has been shown to be chemically reactive in the atmosphere when reacting with hydroxyl radicals and by photolysis. The rate constant for the reaction of methyl ethyl ketone with hydroxyl radicals in the atmosphere at 22-32°C has been reported as follows:

K_{OH} (cm^3 $molecule^{-1}$ sec^{-1})	Reference
3.4×10^{-12}	Winer et al., 1976
2.6×10^{-12}	Cox et al., 1980
0.94×10^{-12}	Atkinson et al., 1982

Assuming an average atmospheric hydroxyl radical concentration of 10^6 molecules/cm^3, the rate constants can be used to calculate a half-life ranging from ~2.5-8.5 days. The primary product formed from this reaction is acetaldehyde (Cox et al., 1981); however, in the presence of nitrogen oxides and their photooxidation derivatives in the air, PAN (peroxyacetyl nitrate) and CH_3ONO_2 are also formed (Cox et al., 1980, 1981).

Cox et al. (1981) calculated the rate constant for the direct photolysis of methyl ethyl ketone in the atmosphere to be 12.5×10^{-6} sec^{-1}, based on the overlap of the solar spectrum with the absorption spectra at a solar zenith angle of 30°. In addition, the quantum yield for the photodissociation was assumed to be unity; therefore, the rate constant is an upper limit quantity. Based on this rate constant, a photolysis half-life of 15.4 hours is calculated. Lissi et al. (1973) experimentally measured a photodecomposition quantum yield of 0.95 for methyl ethyl ketone, indicating that the above calculation is relatively accurate in assuming a quantum yield of unity. Graedel (1978) reported a similar methyl ethyl ketone photolysis

rate constant of 14×10^{-6} sec^{-1}. Hustert and Parlar (1981) also reported rapid photolytic degradation of methyl ethyl ketone in the gas phase by measuring a 51.8% decomposition rate in 2 hours following irradiation of 100 ppm methyl ethyl ketone with a Hg lamp at wavelengths >230 nm.

Methyl ethyl ketone has also been found to be reactive in various smog chamber studies (Levy, 1973; Dilling et al., 1976; Yanagihara et al., 1977; Dimitriades and Joshi, 1977; Farley, 1977; Laity et al., 1973).

Two atmospheric physical removal processes may have some minor importance for methyl ethyl ketone. Dissolution removal (wet deposition) by rainfall may be possible because methyl ethyl ketone is highly water soluble; methyl ethyl ketone has been detected in ambient cloudwater and in ice (Grosjean and Wright, 1983) as well as in rainwater (Kato et al., 1980). Cupitt (1980) suggested that vapor-phase removal of airborn organics by adsorption to aerosol particles is a reasonable mechanism for compounds with a saturation vapor pressure of $\leq 10^{-7}$ mm Hg; methyl ethyl ketone has a vapor pressure of nearly a billion times higher than 10^{-7} mm Hg. Methyl ethyl ketone, however, has been detected in airborn dust and particulates (Dmitriev et al., 1984; Grosjean, 1982).

2.3. SOIL

With the exception of several pure culture studies using microbes isolated from soil, the fate of methyl ethyl ketone in soil has not been experimentally investigated. The aerobic soil bacterium, Nocardia LSU-169, has been found to convert methyl ethyl ketone into the intermediates ethyl acetate and ethanol during metabolism (Eubanks, 1973). A strain of Brevibacterium and Mycobacterium vaccae (JOB5) has been found to be able to degrade methyl ethyl ketone to a proprionate product (Perry, 1968; Phillips and Perry, 1974). Nocardia sp. 249, which is able to utilize butadiene as a

sole carbon source, was not able to grow on methyl ethyl ketone (Watkinson and Somerville, 1976), and various Candida yeast strains were also unable to utilize methyl ethyl ketone (Lowery et al., 1968).

Methyl ethyl ketone undergoes direct photolysis in the atmosphere (see Section 2.2.) and has been shown to be an effective photosensitizer (see Section 2.1.3.); therefore, photolysis of methyl ethyl ketone on soil surfaces is possible. While the relative importance of soil photolysis is uncertain, it is not likely to be as significant as volatilization.

The relatively high vapor pressure of methyl ethyl ketone (98.0 mm Hg at 25°C) suggests that it will evaporate quite rapidly from solid surfaces to which it is not tightly adsorbed. As noted below, methyl ethyl ketone is not predicted to have strong soil adsorbance. Therefore, it is likely to evaporate quickly from dry soil surfaces. Evaporation from moist soils is more difficult to estimate; however, methyl ethyl ketone has been shown to volatilize from water solutions quite rapidly (see Section 2.1.5.).

Although experimental leaching studies regarding methyl ethyl ketone are not available, its soil mobility can be predicted by several methods. The K_{oc} of an organic compound can be estimated from its WS by using the following equation developed by Kenaga and Goring (1978): Log K_{oc} = 3.64-0.55 Log WS (in ppm). From a WS of 268,000 ppm, the K_{oc} value is calculated to be 4.5. Prediction from the K_{ow} can be done by using the Kenaga and Goring (1978) equation: Log K_{oc}=0.544 Log K_{ow}+1.377; this yields a calculated K_{oc} value of 34. Prediction from the molecular topology and quantitative structure-activity relationship method of Sabljic (1984) yields a K_{oc} value of 50. A K_{oc} value of $\leq$50 indicates high soil mobility. Therefore, methyl ethyl ketone may be expected to be susceptible to significant leaching in many types of soil. Methyl ethyl ketone has been

detected in leachates from landfill sites (Sawhney and Kozloski, 1984; Francis et al., 1980).

2.4. SUMMARY

Methyl ethyl ketone will apparently not accumulate in aquatic, atmospheric, or soil environments because of its reactivity under environmental conditions. When exposed to the ambient environment, methyl ethyl ketone is susceptible to relatively rapid removal and will not persist in the environment. In the aquatic environment, methyl ethyl ketone is susceptible to significant degradation by photolysis and microbial decomposition. Methyl ethyl ketone is also susceptible to transport into the atmosphere by volatilization. Hydrolysis and oxidation of methyl ethyl ketone in water are not important processes, and methyl ethyl ketone is not expected to bioaccumulate in aquatic organisms.

Once exposed to the sunlit atmosphere, methyl ethyl ketone is subject to rapid removal by direct photolysis and reaction with hydroxyl radicals; atmospheric half-lives of <1 day can be calculated from available kinetic rate data. Methyl ethyl ketone has been detected in rain and cloudwater. Therefore, some removal by rainfall is possible.

Soil microorganisms are capable of degrading methyl ethyl ketone; however, because of the lack of appropriate experimental data, the rate at which this occurs in the environment is not clear. Methyl ethyl ketone is susceptible to surface photolysis and will apparently evaporate quite rapidly from soil. It is also susceptible to significant leaching and has been detected in leachates from landfills.

3. EXPOSURE

3.1. WATER

Methyl ethyl ketone has been detected in a variety of waters, including drinking water. Sawhney and Kozloski (1984) found levels of 4.8-8.2 mg/ℓ methyl ethyl ketone in leachate from the Southington, CT landfill site. A survey of federal studies showed that methyl ethyl ketone was found in <5% of all groundwaters examined (Dyksen and Hess, 1982). Methyl ethyl ketone was detected (no concentration reported) in the drinking water of the following cities: Tuscaloosa, AL (Bertsch et al., 1975); Cincinnati, OH; Miami, FL; Ottumwa, IA; Philadelphia, PA; Seattle, WA (Coleman et al., 1976) and Washington, DC (Scheiman et al., 1974). Lande et al. (1976) reported that methyl ethyl ketone was identified in raw and finished, potable waters and in industrial wastewaters in the Mississippi River in Louisiana. Fielding et al. (1981) qualitatively detected methyl ethyl ketone in 3 of the 14 treated water supplies surveyed in England.

Jungclaus et al. (1978) detected methyl ethyl ketone levels of 8-20 ppm in wastewaters from a specialty chemical manufacturing plant located alongside the Brackish River, but did not detect it in downstream river water or sediment. Dojlido (1977) reported a concentration of >100 ppm in wastewater from a synthetic leather plant in Poland. Corwin (1969) detected methyl ethyl ketone in seawater; levels of 0-22 ppb were found in straits of Florida seawater while levels of 0-8 ppb were found in eastern Mediterranean seawater. Ewing et al. (1977) examined 14 heavily industrialized river basins in the United States for organic pollutants; methyl ethyl ketone was detected at a level of 23 ppb in only one of 204 sites sampled. Sauer (1981) identified 1.5 ppm concentrations of methyl ethyl ketone in vented surface water discharges from offshore production operations in the Gulf of

Mexico. Francis et al. (1980) identified methyl ethyl ketone in leachates from low-level radioactive waste disposal sites at Maxey Flats, KY and West Valley, NY.

The gross analysis available from the U.S. EPA STORET Data Base contains 262 observations for methyl ethyl ketone in water with a mean concentration of 399 µg/ℓ and minimum and maximum concentrations of 0 and 10,000 µg/ℓ, respectively. Four dry-weight sediment observations yielded a mean concentration of 5788 µg/kg with minimum and maximum concentrations of 50 and 23,000 µg/kg, respectively.

3.2. FOOD

Pellizzari et al. (1982) detected methyl ethyl ketone in 5 of 8 samples of mother's milk collected in Bridgeville, PA, Bayonne, NJ, Jersey City, NJ and Baton Rouge, LA. The ketones are minor components of a wide number of foods. It has been detected in Swiss cheese (0.3 ppm), cream (0.154-0.177 ppm) and milk fat (8.0 ppm). It was also found in roasted barley, bread, honey, chicken, oranges, black tea and rum (Lande et al., 1976).

3.3. INHALATION

Exposure of methyl ethyl ketone to the atmosphere can result from a variety of sources. Graedel (1978) identified the following emission sources from a literature review: automobile exhaust, forest fires, industrial emissions, insects, printing, solvent evaporation, tobacco smoke, wood pulping emissions and turbine engine emissions. Methyl ethyl ketone has also been detected (not quantified) in the atmosphere of a shale oil wastewater facility (Hawthorne and Sievers, 1984), in emissions from a garbage disposal facility (Kamiya and Ose, 1981) and in emissions from fermentation plants (Furutani et al., 1979).

Some ambient monitoring for methyl ethyl ketone has been reported. Grosjean and Wright (1983) detected methyl ethyl ketone levels of 0-0.47 µg/mℓ in cloudwater from Henninger Flats, CA, while Grosjean (1982) detected methyl ethyl ketone levels as high as 14 ppb in Los Angeles air during a severe smog episode in 1980. Pellizzari (1982) found methyl ethyl ketone at concentrations ranging from a trace to 33 µg/m³ in air surrounding a waste disposal site in Edison, NJ. Bozzelli et al. (1980,) examined the ambient air in Rutherford, Newark, Elizabeth, South Amboy, Pine Barrens, and Camden, NJ for methyl ethyl ketone but detected no concentrations above the detection limits (0.01 ppb) with GC-FID; however, methyl ethyl ketone was qualitatively detected by MS in the sample from Rutherford. During an air pollution episode in Japan, a methyl ethyl ketone level of 4.33 ppb was detected in ambient air (Anonymous, 1978). Jarke et al. (1981) identified methyl ethyl ketone in both indoor and outdoor air from 3 of 36 metropolitan Chicago area homes studied.

Methyl ethyl ketone can be produced in ambient air by the photooxidation of butane or other hydrocarbons (Cox et al., 1981; Carter et al., 1979a,b); this is another atmospheric source of methyl ethyl ketone.

3.4. DERMAL

Pertinent data regarding dermal exposure to methyl ethyl ketone were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

The peak blood level of methyl ethyl ketone (0.95 mg/mℓ) was reached within 4 hours following oral administration of the chemical in water at 1690 mg/kg to male rats (Dietz et al., 1981; Dietz and Traiger, 1979), indicating that methyl ethyl ketone was absorbed from the GI tract.

In a group of workers exposed to n-hexane, 2-methylpentane, 3-methylpentane, methylcyclopentane, cyclohexane and acetone, as well as ≤300 µg/ℓ of methyl ethyl ketone, Perbellini et al. (1984) reported that 70% of the inhaled methyl ethyl ketone was retained in the alveolar space. Perbellini et al. (1984) also reported that the mean blood concentration of methyl ethyl ketone in these workers was 2630±2450 µg/ℓ (range: 842-9573 µg/ℓ). The environmental concentration was significantly correlated with the alveolar concentration of methyl ethyl ketone, which was, in turn, significantly correlated with blood levels of methyl ethyl ketone. The urine of workers exposed to a mean concentration of methyl ethyl ketone in air of 101±67 µg/ℓ contained a mean concentration of methyl ethyl ketone of 487±277 µg/ℓ at the end of the 8-hour work shift (Perbellini et al., 1984). Miyasaka et al. (1982) found that the urinary levels of methyl ethyl ketone in occupationally exposed workers increased rapidly during the first 2 hours of the 8-hour work shift. Therefore, methyl ethyl ketone was rapidly absorbed following occupational exposure.

4.2. DISTRIBUTION

As determined by Perbellini et al. (1984), the solubility of methyl ethyl ketone in various human tissues appeared similar in all tissues examined (Table 4-1). Perbellini et al. (1984) concluded that their data suggested that methyl ethyl ketone did not accumulate in the body tissues.

TABLE 4-1

Methyl Ethyl Ketone Solubility in the Human Tissues[a,b]

Tissues	Tissue/Air[c]	Tissue/Blood[d]
Blood	183 ± 12	1
Kidney	197 ± 17	1.05
Liver	180 ± 15	0.98
Brain	168 ± 26	0.92
Fat	161 ± 14	0.88
Muscle	212 ± 30	1.16
Heart	254 ± 25	1.39
Lung	147 ± 9.6	0.8

[a]Source: Perbellini et al., 1984

[b]Human tissue was obtained from two workers who died from heart attacks during the study.

[c]These numbers are the tissue/air partition coefficients of methyl ethyl ketone.

[d]These numbers are, presumably, the tissue/blood partition coefficients of methyl ethyl ketone.

4.3. METABOLISM

Groups of male guinea pigs received an intraperitoneal injection of 450 mg/kg of methyl ethyl ketone (DiVincenzo et al., 1976). Methly ethyl ketone, 3-butanol, 3-hydroxy-2-butanone and 2,3-butanediol were identified by GC/MS in the serum from blood taken 1, 2, 4, 6, 8, 12 and 16 hours after dosing. The half-life of methyl ethyl ketone in serum was reported to be 270 minutes and the clearance time was 12 hours. The metabolic pathway illustrated in Figure 4-1 was proposed by DiVincenzo et al. (1976).

Male Sprague-Dawley rats were treated orally with 1690 mg/kg of a 21.0% aqueous solution of methyl ethyl ketone (Dietz and Traiger, 1979; Deitz et al., 1981). The levels of 2-butanol, 3-hydroxy-2-butanone and 2,3-butanediol that were detected by GC in rat blood 4 and 18 hours after dosing are given in Table 4-2. Dietz and Traiger (1979) concluded that methyl ethyl ketone metabolism in the rat was similar to methyl ethyl ketone metabolism in the guinea pig as reported by DiVincenzo et al. (1976), and that methyl ethyl ketone underwent oxidative hydroxylation to form 3-hydroxy-2-butanone, which was subsequently reduced to 2,3-butanediol.

4.4. EXCRETION

The urine from an unspecified group of workers occupationally exposed to methyl ethyl ketone, cyclohexane and acetone was collected at the end of an 8-hour work shift, and the urinary levels of methyl ethyl ketone and 3-hydroxy-2-butanone (acetylmethylcarbinol) were determined by GC (Perbellini et al., 1984). In workers exposed to a mean of 101±67 µg/ℓ (range: 8-272 µg/ℓ) of methyl ethyl ketone, the mean urinary concentration of methyl ethyl ketone was 487±277 µg/ℓ (range: 120-1120 µg/mℓ). Although 3-hydroxy-2-butanone was not identified in the urine of workers exposed to the lowest levels of methyl ethyl ketone, it was

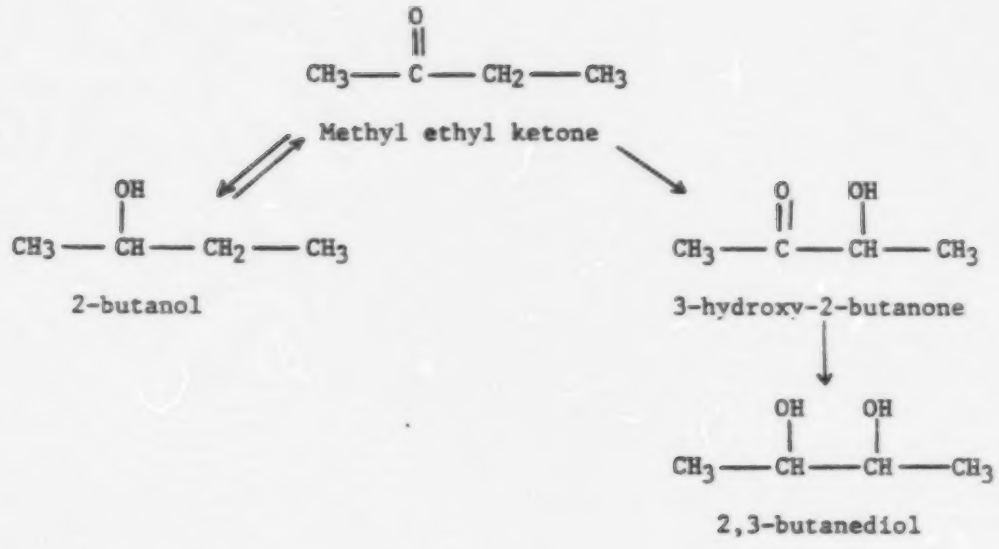


FIGURE 4-1

Proposed Metabolic Pathway for Methyl Ethyl Ketone
in the Guinea Pig

Source: DiVincenzo et al., 1976

TABLE 4-2

Blood Concentration of 2-Butanone and Its Metabolites
Following Administration of Methyl Ethyl Ketone[a]

Time (hours)	Methyl Ethyl Ketone (mg/100 mℓ)	2-Butanol (mg/100 mℓ)	3-Hydroxy-2-butanone (mg/100 mℓ)	2,3-Butanediol[b] (mg/100 mℓ)
4	94.1 ± 10.8	3.2 ± 0.2	2.4 ± 0.2	8.1 ± 0.4
18	6.2 ± 1.5	0.6 ± 0.1	1.4 ± 0.2	25.6 ± 0.5

[a]Source: Dietz and Traiger, 1979

[b]Each value represents the mean ± S.E. for a group of four animals

identified in the urine of workers exposed to higher levels and was significantly correlated with both the level of occupational exposure to methyl ethyl ketone and with the urinary concentration of methyl ethyl ketone (Perbellini et al., 1984; Brugnone et al., 1983).

Miyasaka et al. (1982) reported in an abstract that urinary levels of methyl ethyl ketone increased rapidly within the first 2 hours of an 8-hour shift to the plateau of maximum concentration observed in male workers industrially exposed to methyl ethyl ketone. The pre-shift levels of methyl ethyl ketone in the urine were low. The levels of methyl ethyl ketone correlated with the measured levels of methyl ethyl ketone in the air (Miyasaka et al., 1982).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of methyl ethyl ketone by oral and inhalation routes of exposure were not located in the available literature as cited in the Appendix. Methyl ethyl ketone is not scheduled for testing by the National Toxicology Program NTP, (1984). As reviewed by Lande et al. (1976), no tumors were observed on the skin of mice after 50 mg of methyl ethyl ketone had been applied twice weekly for 1 year (Horton et al., 1965).

5.2. MUTAGENICITY

As summarized in Table 5-1, methyl ethyl ketone was negative for reverse mutation in Salmonella typhimurium strains TA98, TA100, TA1535 or TA1537 with or without metabolic activation (Florin et al., 1980; Douglas et al., 1980). Nestmann et al. (1980) reiterated the results described by Douglas et al. (1980); in these two studies, methyl ethyl ketone was identified as a component in the effluents from a pulp and paper mill.

5.3. TERATOGENICITY

Groups of Sprague-Dawley rats were exposed by inhalation to nominal concentrations of 0 ppm (n=47), 1000 ppm (2949 mg/m^3) (n=29) or 3000 ppm (8848 mg/m^3) (n=21) of methyl ethyl ketone for 7 hours/day on days 6-15 of gestation (Schwetz et al., 1974). The day that vaginal smears were sperm positive was designated day 0 of gestation. Maternal body weight, conception rate, litter size, maternal SGPT levels, absolute or relative liver weight and behavior were not affected by exposure to methyl ethyl ketone at any level tested. As indicated in Tables 5-2 and 5-3, there was a significant decrease in fetal body weight and length and a significant increase in the percentage of litters with at least one fetus with a skeletal anomaly at

TABLE 5-1

Mutagenicity of Methyl Ethyl Ketone
(Reverse mutation assay)

Indicator/ Organism	Concentration/ Dose	Application Method	Activation System	Response	Comment	Reference
Salmonella typhimurium TA98 TA100 TA1535 TA1537	3 µmol/plate	spot test	+/- S9	-/-	NC	Florin et al., 1980
S. typhimurium TA98 TA100 TA1535 TA1537	≤10 mg/plate	NR	+/- S9	-/-	Because of its low solubility, methyl ethyl ketone was not lethal to the bacteria at doses ≤10 mg/plate	Douglas et al., 1980; Nestmann et al., 1980

NC = No comment; NR = not reported

TABLE 5-2

Effects of Methyl Ethyl Ketone Inhaled During Pregnancy in Rats[a]

Factors	Control	1000 (ppm)	3000 (ppm)
Number of litters	43	23	21
Percent pregnancy (pregnant/bred)	91 (43/47)	79 (23/29)	100 (21/21)
Corpora lutea/dam	14±2	14±3	14±3
Implantation sites/litter	11±3	12±3	12±3
Live fetuses/litter	11±3	11±3	12±3
Resorptions/implantation sites (%)	34/492 (7%)	15/268 (6%)	15/257 (6%)
Litters with resorptions (%)	19/43 (44%)	12/23 (52%)	10/21 (48%)
Litters totally resorbed	0/43	0/23	0/21
Resorptions/litters with resorptions	34/19	15/12	15/10
Fetal body weight (g)	5.64±0.34	5.34±0.28[b]	5.45±0.16
Fetal crown-rump length (mm)	43.7±1.0	42.3±0.7[b]	43.1±0.6

[a]Source: Schwetz et al., 1974

[b]Statistically significantly different from controls by an analysis of variance and Dunnett's test ($p<0.05$)

TABLE 5-3

The Number of Rat Litters (% of Total Litters Affected) Containing at Least One Fetus with a Malformation or a Developmental Anomaly after Methyl Ethyl Ketone Inhalation by Dams during Pregnancy[a]

Factors	Control	1000 (ppm)	3000 (ppm)
Number of litters examined	43	23	21
Gross malformations[b] (%)	0	0	4 (19)[c]
Skeletal:			
Delayed ossification in the skull (%)	5 (12)	5 (23)	0
Lumbar ribs or spurs (%)	10 (24)	6 (27)	8 (38)
Bipartite centra (%)	9 (21)	4 (18)	7 (33)
Bipartite sternebrae (%)	14 (61)	15 (68)	NR
Sternebral delayed ossification (%)	2 (11)	NR	9 (43)
Total skeletal anomalies (%)	25 (58)	21 (95)[c]	17 (81)
Soft tissue:			
Subcutaneous edema (%)	14 (33)	2 (9)	10 (48)
Dilated ureters (%)	5 (12)	4 (30)	5 (24)
Total soft tissue anomalies (%)	22 (51)	16 (70)	16 (76)[c]

[a]Source: Schwetz et al., 1974

[b]Two brachygnathous and 2 acaudate fetuses (with imperforate anus)

[c]Statistically significantly different from controls using the Fisher Exact Probability Test ($p<0.05$)

the 1000 ppm level. No significant change in fetal body weight or length in the percentage of litters with at least one fetal skeletal anomaly was reported at 3000 ppm. An increased incidence of soft tissue as well as sternebral skeletal anomalies occurred, however, at 3000 ppm, as discussed below. No other significant effects were reported in the dams or the pups of dams treated with methyl ethyl ketone at the 1000 ppm exposure levels.

In the group of pregnant rats exposed to 3000 ppm of methyl ethyl ketone, four litters each contained one malformed fetus (see Table 5-3). Two of the malformed fetuses were brachygnathous and two were acaudate with imperforate anus. The incidence of malformed fetuses was significantly increased in the offspring of pregnant rats exposed to 3000 ppm methyl ethyl ketone. In addition, although the incidence of neither subcutaneous edema nor dilated ureter was significantly increased after maternal exposure to 3000 ppm of methyl ethyl ketone, considered together there was a significant increase in the incidence of soft tissue anomalies in the offspring of rats exposed to 3000 ppm of methyl ethyl ketone as indicated in Table 5-2. Delayed ossification also occurred at a higher incidence in the offspring of rats exposed to 3000 ppm of methyl ethyl ketone during pregnancy. Schwetz et al. (1974) concluded that methyl ethyl ketone was fetotoxic and potentially teratogenic, but not maternotoxic, when pregnant rats were exposed to 1000 or 3000 ppm on days 6-15 of gestation.

In an experiment designed to confirm and clarify the results of the Schwetz et al. (1974) study, groups of 25 pregnant Sprague-Dawley rats, weighing 234-332 g, were exposed by inhalation to 400, 1000 or 3000 ppm (1180, 2949 or 8848 mg/m^3) of methyl ethyl ketone for 7 hours/day on days 6-15 of gestation (Deacon et al., 1981). The control group consisted of 35

pregnant rats. The rats were delivered by Cesarean section on day 21 of gestation. No maternal effects were reported at the two lower concentrations.

The body weight gain was decreased and the water consumption was increased in pregnant rats exposed to 3000 ppm of methyl ethyl ketone on days 6-15 of gestation. The pregnancy rate, the resorption rate and the average number of implantations and live fetuses per pregnant rat were not affected by methyl ethyl ketone inhalation at any exposure level tested. As indicated in Table 5-4, there were five fetuses among all groups that had at least one malformation upon examination for external and soft tissue malformations, as follows: There were two severely deformed fetuses with multiple birth defects; one was in the control group and one was in the high exposure group (3000 ppm). One fetus in the low exposure group (400 ppm) had a rotated and adducted forepaw. One fetus from the middle exposure group (1000 ppm) and one from the high exposure group (3000 ppm) had a missing innominate artery. Because of the low incidence and distribution of the malformations observed in the pups of dams exposed to methyl ethyl ketone during pregnancy, Deacon et al. (1981) concluded that, within the limits of the experiment, methyl ethyl ketone was not teratogenic in rats. Fetotoxicity, however, was indicated by an increased incidence of extra ribs and of delayed ossification in the cervical centra (see Table 5-4) at the high exposure level (3000 ppm), but not at either of the two lower exposure levels (Deacon et al., 1981).

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of methyl ethyl ketone were not located in the available literature as cited in the Appendix.

TABLE 5-4

Incidence of Fetal Alterations Among Rats Inhaling Methyl Ethyl Ketone[a]

Factors	Methyl Ethyl Ketone (ppm)[b]			
	0	400	1000	3000
	No. Fetuses Examined/No. Litters Examined			
External and skeletal examination	329/26	238/19	226/19	231/18
Soft-tissue examination	111/26	80/19	78/19	79/18
Bones of the skull	218/26	157/19	148/19	150/18
	No. Fetuses (Litters) Affected			
External examination				
Multiple defects	1(1)[c]	0	0	1(1)[d]
Rotated and adducted forepaw	0	1(1)	0	0
Soft-tissue examination				
Innominate artery missing	0	0	1(1)	1(1)
Skeletal examination				
Skull, delayed ossification[e]	26(14)	19(10)	23(8)	6(4)[f]
Ribs, extra[e]	2(2)	0	0	7(6)[g]
Cervical centra, delayed ossification[e]	83(22)	58(15)	44(16)	114(18)[g]
Total major malformations	1(1)	1(1)	1(1)	2(2)

[a]Source: Deacon et al., 1981

[b]Rats inhaled 0, 400, 1000, or 3000 ppm of methyl ethyl ketone from days 6-15 of gestation.

[c]This fetus exhibited acaudia, imperforate anus, short trunk, ectopic ovary, diaphragmatic hernia, and multiple vertebral defects, including missing ribs, vertebrae, and centra.

[d]This fetus exhibited acaudia, imperforate anus, short trunk, ectopic ovary, and multiple skeletal defects including asymmetric pelvis, fused ribs and missing ribs, vertebrae, and centra.

[e]This alteration was considered to be a skeletal variant and was not included in the calculation of the total malformed fetuses.

[f]Significantly lower than control value by a modified Wilcoxon test, $p<0.05$.

[g]Significantly higher than control value by a modified Wilcoxon test, $p<0.05$.

5.5. CHRONIC TOXICITY

Groups of 15 male and 15 female Fischer 344 rats were exposed by inhalation to 0, 1250, 2500 or 5000 ppm (0, 3687, 7373 or 14,746 mg/m^3) of methy ethyl ketone for 6 hours/day, 5 days/week for 13 weeks (Cavender et al., 1983). The mean body weight in both male and female rats was increased at the low- and mid-exposure levels and decreased at the high-dose level. At the 5000 ppm exposure level, there was an increase in absolute liver weight, in the liver-to-body weight ratio, in the liver-to-brain weight ratio and in the mean corpuscular hemoglobin level in both male and female rats. There was an increase in the kidney-to-body weight ratio and volume of urine and a decrease in the absolute weight of the spleen and the brain in the male rats exposed at 5000 ppm. In the female rats exposed at 5000 ppm, there was a decrease in the brain-to-body weight ratio and a subsequent increase in the kidney-to-brain weight ratio. Increases in the blood levels of alkaline phosphatase, potassium and glucose also occurred at 5000 ppm. The only effect that was reported at the 2500 ppm exposure level was an increase in SGPT in female rats. No significant differences from methyl ethyl ketone exposure (1250, 2500 or 5000 ppm) were observed in food consumption or in opthalmological or neurological functioning and no treatment-related histo- pathologic lesions were observed after 13 weeks of exposure (Cavender et al., 1983).

Five male Wistar rats were exposed by inhalation to methyl ethyl ketone for 8 hours/day, 7 days/week for 15 weeks (Altenkirch et al., 1978, 1979). The initial exposure level of 10,000 ppm (29,493 mg/m^3) of methyl ethyl ketone was reduced to 6000 ppm (17,696 mg/m^3) within a few days of dosing after severe irritation developed in the upper respiratory tract. Although no clinical or morphological signs of axonopathy were reported in the rats

treated with methyl ethyl ketone, all the animals died during week 7 of the experiment, apparently from severe bronchopneumonia. Altenkirch et al. (1978) reported that when they repeated the experiment of exposing rats to methyl ethyl ketone, all the rats died, again presumably from pneumonia.

Groups of eight Wistar male rats were exposed daily to 0 or 200 ppm (590 mg/m^3) of methyl ethyl ketone in air for 12 hours/day for 24 weeks (Takeuchi et al., 1983). The body weight, MCV, DL and MNCV were measured before treatment and every 4 weeks after the experiment started. At the end of 24 weeks, the tail nerve of one rat of each group was examined histologically. Although the MCV and the MNCV were significantly increased and the DL was significantly decreased, after 4 weeks of methyl ethyl ketone exposure, all the parameters evaluated were not significantly different from controls at any other point during the experiment. Takeuchi et al. (1983) compared this transient effect of methyl ethyl ketone with a similar transient effect described by Savolainen and Seppalainen (1980) in rats exposed to 300 ppm of toluene and suggested that methyl ethyl ketone may affect the axonal membrane and cause a transient increase in the MCV.

A group of 25 rats were exposed by inhalation to 235$\pm$26 ppm (693$\pm$77 mg/m^3) of methyl ethyl ketone for 7 hours/day, 5 days/week for 12 weeks (La Belle and Brieger, 1955). Although the growth of the rats exposed to methyl ethyl ketone was reported to be 95 g and the growth of the control rats was reported to be 135 g, no statistical analysis of the data was provided. No gross or microscopic pathology and no effects on hematological parameters were observed. Guinea pigs presumably exposed to the same level of methyl ethyl ketone displayed no adverse effects from the treatment (La Belle and Brieger, 1955).

As summarized in Remington and Basu (1984), no effect on the incidence and extent of paralysis was observed in rats exposed continuously to 1125 ppm (3318 mg/m³) of methyl ethyl ketone for 5 months (Saida et al., 1975). The effect of 0, 125, 250, 500 or 1000 ppm of methyl ethyl ketone for an unspecified number of hours/day and days/week was reported to have no effect on rats or guinea pigs (Mellon Institute, 1950).

No signs of neurotoxicity or axonopathy were reported in cats that were treated subcutaneously with methyl ethyl ketone twice daily, 5 days/week for up to 8.5 months (Spencer and Schaumberg, 1976).

An abstract of an Italian study (Freddi et al., 1982) reported that distal axonopathy, but no neuropathy, was present in workers after long-term occupational exposure to methyl ethyl ketone.

Eye, skin and respiratory irritation, as well as headache, nervous system disorders and hepatic insufficiency were reported in abstracts of studies evaluating the effects of occupational exposure to mixtures of solvents and toxic chemicals including methyl ethyl ketone (McLouth, 1981; Markel and Slovin, 1981; Tangredi et al., 1981).

5.6. OTHER RELEVANT INFORMATION

The ACGIH (1980) reported that Smyth et al. (1962) indicated that the oral LD_{50} in rats was 6.86 mℓ/kg. Kimura et al. (1971) reported LD_{50} values of 3.1, 3.6 and 3.4 mℓ/kg of methyl ethyl ketone for 14-day-old rats, young adult rats and older adult rats, respectively. Exposure of mice to methyl ethyl ketone at an unspecified concentration caused a 50% decrease in the respiratory rate, the RD_{50} (DeCeaurriz et al., 1981). Based on their experimental data, DeCeaurriz et al. (1981) predicted that human exposure to 1075 ppm of methyl ethyl ketone would be uncomfortable but tolerable at 0.1 RD_{50} and that human exposure to 108 ppm would produce minimal or no effect at 0.01 RD_{50}.

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Groups of four male guinea pigs were treated intraperitoneally with 750, 1500 or 2000 mg/kg of methyl ethyl ketone and evaluated 24 hours after dosing (DiVincenzo and Krasavage, 1974). The low dose resulted in a serum ornithine carbamyl transferase activity level of 1.5 accompanied by no hepatic histopathology and questionable hepatocyte lipid accumulation. Although no hepatic histopathology was reported at the middle (1500 mg/kg) or high (2000 mg/kg) dose levels, serum ornithine carbamyl transferase activity was elevated to 4.5 and 10.8, respectively, and lipid accumulation was reported in the hepatocytes. One of the four animals in the high dose group died (DiVincenzo and Krasavage, 1974). An abstract of the work of Wagner et al. (1983) indicated that there was a time- and dose-related increase in the hepatic microsomal microoxygenases in rats chronically exposed to mixtures of hexane and methyl ethyl ketone. An abstract of the work of Hewitt et al. (1983) reported that the oral administration of methyl ethyl ketone potentiated the hepatotoxicity of CCl_4 administered 18 hours later by intraperitoneal injection of male rats.

Methyl ethyl ketone potentiated the effect of n-hexane on the alveolar epithelium of rats exposed to the mixture for 8 hours/day for up to 89 days (Schnoy et al., 1982). Although no histopathology was evident with the light microscope, Schnoy et al. (1982) described fatty deposits in pneumocyte I and II cells.

Ketones have been reported to cause nervous system depression and neurotoxicity (Beall and Ulsamer, 1981). Although methyl ethyl ketone does not appear to be cytotoxic or neurotoxic alone (Dick et al., 1984; Takeuchi et al., 1983; Selkoe et al., 1978), it potentiates the neurotoxicity of n-hexane (Takeuchi et al., 1983; Altenkirch et al. 1982a,b), ethyl-n-butyl ketone (O'Donoghue et al., 1984) and methyl n-butyl ketone (Spencer and Schaumberg, 1976; Saida et al., 1975).

An abstract of the work of Ziegenmeyer et al. (1976) indicated that methyl ethyl ketone enhanced the effect of anesthetics absorbed percutaneously. Methyl ethyl ketone enhanced the ability of benzo[a]pyrene to induce epidermal hyperplasia (Ingram, 1979). Wahlberg (1984), however, recently reported that the application of methyl ethyl ketone to human skin did not result in an increased blood flow in the hypodermis.

Using the water flea, Daphnia magna, as a test species, the U.S. EPA (1978) and LeBlanc, (1980, 1984) reported that the 24- and 48-hour LC_{50} values were both >519 mg methyl ethyl ketone/ℓ. No observable effect was reported following the 48-hour exposure at 519 mg/ℓ. Bringmann and Kuehn (1982) reported 24-hour EC_0, EC_{50} and EC_{100} values of 2600, 7060 and >10,000 mg/ℓ, respectively, in Daphnia magna exposed to methyl ethyl ketone. In the marine crustacean, Mysidopsis bahia, the 96-hour LC_{50} was >402 mg/ℓ (LeBlanc, 1984). In the aquatic mosquito larvae (Aedes aegypti), the 4-hour LC_{50} was 13 g/ℓ (Kramer et al., 1983).

6.2. CHRONIC EFFECTS

Pertinent data regarding the toxic effects of methyl ethyl ketone to aquatic organisms following chronic exposures were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Bringmann and Kuehn (1978) reported toxicity threshold levels for inhibited cell multiplication at 120 and 4300 mg methyl ethyl ketone/ℓ, respectively, in a blue-green algae (Microcystis aeruginosa) and a green algae (Scenedesmus quadricanda). Algal cultures were exposed to the toxicant for 8 days before growth was determined turbidimetrically. LeBlanc (1984) reported that the 96-hour LC_{50} values in the freshwater algae, Selenastrum capricornutum, and the marine algae, Skeletonema costatum, were >500 mg methyl ethyl ketone/ℓ.

6.4. RESIDUE

Pertinent data regarding the residue of methyl ethyl ketone in aquatic organisms or the aquatic environment were not located in the available literature as cited in the Appendix.

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Pertinent data regarding the toxic effects of methyl ethyl ketone to aquatic organisms following chronic exposures were not located in the available literature cited in the Appendix.

6.3. PLANT EFFECTS

Bringmann and Kuehn (1978) reported toxicity threshold levels for inhibited cell multiplication at 120 and 4300 mg methyl ethyl ketone/ℓ, respectively, in a blue-green algae (Microcystis aeruginosa) and a green algae (Scenedesmus quadricanda). Algal cultures were exposed to the toxicant for 8 days before growth was determined turbidimetrically. LeBlanc (1984) reported that the 96-hour LC_{50} values in the freshwater algae, Selenastrum capricornutum, and the marine algae, Skeletonema costatum, were >500 mg methyl ethyl ketone/ℓ.

6.4. RESIDUE

Pertinent data regarding the residue of methyl ethyl ketone in aquatic organisms or the aquatic environment were not located in the available literature cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Bringmann and Kuehn (1980) reported that the toxicity threshold levels of methyl ethyl ketone that caused inhibition of cell multiplication were 1150 and 190 mg/ℓ in the bacteria, Pseudomonas putida, and protozoan, Entosiphon sulcatum. Tests were conducted for 16 hours with bacteria and 72 hours using protozoa. Curtis et al. (1982) reported a 5-minute EC_{50} for decreased bacterial bioluminescence (Photobacterium phosphoreum) at 5050 mg methyl ethyl ketone/ℓ. This test suggestively approximates 96-hour LC_{50} values in fish.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The TWA-TLV of 200 ppm (590 mg/m³) and the STEL of 300 ppm (885 mg/m³) for occupational exposure to methyl ethyl ketone, reported by the ACGIH (1983), was based on a Manufacturing Chemists Association (1968) report indicating that human exposure to 590 mg/m³ of methyl ethyl ketone resulted in eye and nose irritation in ~50% of those exposed (ACGIH, 1980).

The NIOSH (1978) recommendation and the OSHA standard for occupational exposure to methyl ethyl ketone is 200 ppm (590 mg/m³) for an 8-hour TWA (CFR, 1981).

As summarized in ACGIH (1980), the recommended level of permissible occupational exposure to methyl ethyl ketone is 100 ppm (295 mg/m³) in East Germany (1973), Yugoslavia (1971), Hungary (1974) and the USSR (1966); the recommended level is 150 ppm (442 mg/m³) in Sweden (1974) and 200 ppm in West Germany (1974).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic affects of methyl ethyl ketone were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Adequate carcinogenicity testing of methyl ethyl ketone has not been reported. Methyl ethyl ketone was negative for reverse mutation in four stains of Salmonella typhimurium with or without metabolic activation (Florin et al., 1980; Douglas et al., 1980). Pertinent data regarding other reproductive effects of methyl ethyl ketone were not available as cited in the Appendix.

Schwetz et al. (1974) observed increased incidences of gross malformations (brachygnathous and acaudate fetuses with imperforate anus) delayed sternebral ossification and soft tissue anomalies (subcutaneous edema and dilated ureters) in the offspring of rats exposed by inhalation to 3000 ppm (8848 mg/m^3) methyl ethyl ketone on days 6-15 of gestation. At 1000 ppm (2949 mg/m^3), there was decreased fetal body weight and crown-rump length and an increase in the percentage of litters with $\geq$1 skeletal anomaly. No maternal toxicity was evident. In a subsequent study on the reproducibility of these observations by Deacon et al. (1981), however, the only treatment-related effect on fetuses was an increased incidence of extra ribs and delayed ossification at 3000 ppm (8848 mg/m^3) but not at 1000 or 400 ppm (2949 or 1180 mg/m^3). Maternal toxicity, as evidenced by reduced body weight gain and water consumption of rat dams, was observed at 3000 ppm. Therefore, methyl ethyl ketone appeared to be fetotoxic at inhalation exposures of 1000 and 3000 ppm, and possibly teratogenic and maternotoxic at 3000 ppm.

No chronic oral or inhalation studies of methyl ethyl ketone were found in the available literature; however, several subchronic inhalation studies were available and form an adequate data base for the derivation of an ADI.

Inhalation exposure of rats to methyl ethyl ketone at 6000-10,000 ppm (17,696-29,493 mg/m³), 8 hours/day, 7 days/week, was fatal within 7 weeks (Altenkirch et al., 1978, 1979). Rats exposed by inhalation to 5000 ppm (14,745 mg/m³), 6 hours/day, 5 days/week for 13 weeks had decreased body weight gain, increased organ-to-body weight and organ-to-brain weight ratios of the liver and kidneys, decreased brain-to-body weight ratio, increased mean corpuscular hemoglobin content, increased volume of urine and increased levels of serum alkaline phosphatase, potassium and glucose (Cavender et al., 1983). At 2500 ppm (7373 mg/m³), body weights were increased and there was an increase in SGPT levels. At 1250 ppm (3687 mg/m³), body weight was increased. Takeuchi et al. (1983) found that rats exposed to methyl ethyl ketone by inhalation at 200 ppm (590 mg/m³), 12 hours/day, 7 days/week had increased MCV and MNCV and decreased DL compared with controls after 4 weeks, but the effects were no longer apparent after 24 weeks. The physiologic significance of these transient effects is uncertain. Decreased body weight gain was observed in rats exposed to methyl ethyl ketone at 235 ppm (693 mg/m³), 7 hours/day, 5 days/week for 12 weeks (LaBelle and Brieger, 1955). Although hematologic parameters were measured and gross and histologic examination of organs was performed, no effects were observed.

In a previous determination of the ADI for methyl ethyl ketone, the U.S. EPA (1985) used the study of LaBelle and Brieger (1955) as the basis. The NOAEL of 693 mg/m³, 7 hours/day, 5 days/week was converted to an equivalent human dose of 46 mg/kg/day or 3220 mg/day for a 70 kg man, by multiplying by 7 hours/24 hours and 5 days/7 days to expand from intermittent to continuous exposure, by 0.5 (the absorption coefficient), by 0.223 m³/day/0.35 kg (the rat breathing rate/rat body weight) and assuming an average

human body weight of 70 kg. The equivalent human NOAEL of 3220 mg/day was divided by an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for estimating a chronic exposure and 10 to protect the most sensitive individuals of the human population), resulting in an ADI of 3.2 mg/day.

The exposure of 590 mg/m^3, 12 hours/day, 7 days/week in the study of Takeuchi et al. (1983) is equivalent to a human dose of 6578 mg/day. This dose could also be considered a NOAEL. Since, however, the significance of the effects on MCV, MNCV and DL is uncertain and histologic examination was limited to tail nerve of one rat in each group, it is inappropriate to base an ADI on this study. Therefore, the ADI of 3.2 mg/day is recommended for methyl ethyl ketone.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

No chronic oral or inhalation studies of methyl ethyl ketone were located in the available literature, but several subchronic studies and two teratogenicity studies described effects of inhalation exposure of rats to methyl ethyl ketone, as detailed in Sections 5.3. and 5.5. The data used to calculate MEDs and CSs are presented in Table 9-1. Inhalation exposures were converted to human MEDs by expanding the intermittent exposures to continuous exposure and by multiplying by $(0.35\ kg/70\ kg)^{1/3}$ and 0.223 m^3/0.35 kg as correction factors for rat breathing rate and 70 kg for human weight. For subchronic studies, the exposure was divided by an uncertainty factor of 10 to approximate chronic exposure.

In the first teratogenicity study, exposure of rats to 3000 ppm (8848 mg/m^3) methyl ethyl ketone for 7 hours/day on days 6-15 of gestation resulted in increased incidences of malformed fetuses (brachygnathous and acaudate), soft tissue anomalies and delayed ossification (Schwetz et al., 1974). At 1000 ppm (2949 mg/m^3), fetal body weight and crown-rump length was reduced. In a subsequent study from the same laboratory (Deacon et al., 1981), exposure of rats to 3000 ppm (8848 mg/m^3), 7 hours/day on days 6-15 of gestation did not result in evidence of teratogenicity, although there was evidence of fetotoxicity (extra ribs and delayed ossification) and maternal toxicity (reduced body weight gain). Taken together, these studies indicate that methyl ethyl ketone may be teratogenic at an exposure level (8848 mg/m^3, 7 hours/day) that is toxic to dams. The MED equivalent to this exposure is 19,734 mg/day and corresponds to an RV_d of 1. Teratogenicity with signs of maternal toxicity warrants an RV_e of 9. The CS, which is the product of the RV_d and RV_e, is 9, corresponding to an RQ of 1000.

TABLE 9-1

Composite Scores for Inhalation Toxicity of Methyl Ethyl Ketone in Rats

Exposure	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
3000 ppm (8848 mg/m³) 7 hours/day, days 6-15 of gestation	19,734	1	Malformed fetuses (brachygnathous and acaudates); marginal maternal toxicity (decreased body weight)	9	9	1000	Schwetz et al., 1974; Deacon et al., 1981
1000 ppm (2949 mg/m³) 7 hours/day days 6-15 of gestation	6,566	1	Fetotoxicity (decreased fetal body weight and crown-rump length; skeletal anomalies)	8	8	1000	Schwetz et al., 1974
2500 ppm (7373 mg/m³) 6 hours/day, 5 days/week for 24 weeks	1,004*	1	Increased SGPT	6	6	1000	Cavender et al., 1983
235 ppm (693 mg/m³) 7 hours/day, 5 days/week for 12 weeks	110.4*	2.4	Decreased body weight gain	4	9.6	1000	LaBelle and Brieger, 1955

*The exposure was divided by an uncertainty factor of 10 to approximate chronic exposure

The fetotoxic effects, in the absence of maternal toxicity, observed at 2949 mg/m³, 7 hours/day can also be used to calculate a CS. The MED is 6566 mg/day, corresponding to an RV_d of 1. Fetotoxicity warrants an RV_e of 8; the CS is 8 and the RQ is 1000.

In an inhalation study, rats exposed to 6000-10,000 ppm (17,696-29,493 mg/m³), 8 hours/day, 7 days/week, died within 7 weeks (Altenkirch et al. 1978; 1979). Since the deaths represented an acute response to relatively high exposures, this study is inappropriate for the derivation of the RQ.

In a subchronic study, rats were exposed by inhalation to methyl ethyl ketone at 0, 1250, 2500 or 5000 ppm (0, 3687, 7373 or 14,746 mg/m³), 6 hours/day, 5 day/week for 13 weeks (Cavender et al., 1983). At the 14,746 mg/m³ exposure level, rats had increased organ-to-body weight ratios and increased organ-to-brain weight ratios of kidneys and liver and decreased brain-to-body weight ratio. In addition, mean corpuscular hemoglobin content and the volume of urine were increased, body weight gain was decreased and serum levels of alkaline phophatase, potassium and glucose were increased. Based on increased serum levels of alkaline phosphatase, a clinical manifestation of liver necrosis, the highest RV_e that can be assigned to these effects is 6. At the next lower exposure level of 7373 mg/m³, however, increased levels of SGPT, also a clinical manifestation of liver necrosis, was observed. The MED corresponding to 7373 mg/m³, 6 hours/day, 5 days/week, is 1004 mg/day using an uncertainty factor of 10. The RV_d is 1 and the RV_e is 6, resulting in a CS of 6 and an RQ of 1000.

Rats exposed by inhalation to methyl ethyl ketone at 200 ppm (590 mg/m³), 12 hours/day, 7 days/week for 24 weeks had increased MCV and MNCV and decreased DL after 4 weeks, but not after 24 weeks. The physiologic significance of these changes is not certain. Therefore, it is not appropriate to derive a CS based on such transient effects.

The only effect observed in rats exposed to methyl ethyl ketone vapor at 235 ppm (693 mg/m³), 7 hours/day, 5 days/week for 12 weeks was reduced body weight gain compared with controls (LaBelle and Brieger, 1955), an effect which warrants an RV_e of 4. The human MED is 110 mg/day, corresponding to an RV_d of 2.4. The CS is 9.6 and the RQ is 1000.

As seen from Table 9-1, the highest CS was obtained from the study of Labelle and Brieger (1955) and is recommended as the basis for the RQ (Table 9-2).

In a previous determination of the RQ (U.S. EPA, 1983), the fetotoxic effect at 2949 mg/m³ for 7 hours/day in the teratogenicity study of Schwetz et al. (1974) was used as the basis for the derivation. The human MED was calculated as 860 mg/day (as opposed to 6566 mg/day in the present determination) because an uncertainty factor of 10 was used. The use of an uncertainty factor of 10 in a teratogenicity study is not appropriate, however, because the treatment from days 6-15 of gestation represents chronic exposure to the fetus, but acute exposure to the dam. It is the effect on the fetus, rather than the effect on the dams that should be ranked. Furthermore, the teratogenic effect observed at 8848 mg/m³ was not considered separately from fetotoxicity. In the previous RQ determination (U.S. EPA, 1983), the study of LaBelle and Brieger (1955) was not considered for the RQ derivation, apparently because decreased body weight was overlooked as an effect. It should be noted, however, that regardless of the approach to RQ derivation, the recommended RQ is 1000.

TABLE 9-2

Methyl Ethyl Ketone

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	110 mg/day
Effect:	decreased body weight gain
Reference:	LaBelle and Brieger, 1955
RV_d:	2.4
RV_e:	4
Composite Score:	9.6
RQ:	1000

*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The only available information regarding the carcinogenicity of methyl ethyl ketone was the report that no tumors were observed on the skin of mice treated with dermal applications of methyl ethyl ketone of 50 mg/application, 2 days/weeks for 1 year (Horton et al., 1965). Therefore, a potency factor ($1/ED_{10}$) cannot be derived and methyl ethyl ketone is classified as an U.S. EPA group D chemical; that is, methyl ethyl ketone cannot be classified as to its carcinogenic potential for humans.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December, 1984, with the exception of the TOXLINE, which was searched and kindly supplied by the Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. U.S. EPA, Office Pesticide Programs, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.